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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/398,399	09/17/99	DELENSTARR	G 10981620-1

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IP ADMINISTRATION
LEGAL DEPARTMENT 20BN
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EXAMINER	
SISSON,B	
ART UNIT	**PAPER NUMBER**
1655	8

DATE MAILED: 04/26/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/398,399	DELENSTARR ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *17 February 2000* .

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *1-9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

14) ☒ Notice of References Cited (PTO-892)
15) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
16) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
17) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
18) ☐ Notice of Informal Patent Application (PTO-152)
19) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group II in Paper No. 7 is acknowledged.

Specification

The use of the trademark TRITON, e.g., TRITON X-100, has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the

invention. As presently worded, the method of claim 10 requires one of skill in the art to definitively label a target nucleic acid sequence (step (b)) when the skilled artisan is not even sure that such a sequence is even present. Note step (a) of said Claim 10:

(a) providing an analyte suspected of containing the target nucleotide sequence

The claim recites no method steps for achieving the labeling of that which is only suspected of existing. Even if it were to be present, the method would require certain method steps to be performed yet as claimed, the labeling is to be performed without any method steps. While the target nucleic acid is to be contacted with "features comprising oligophosphodiester probes," such oligophosphodiester probes are not required to be labeled. Accordingly, it appears that one is to render detectable that which is not detectable. In looking at claims 12 and 13 it can be seen that the target sequence is to be either directly or indirectly labeled.

In looking to claim 10 it is seen that the skilled artisan it so detect the signal from the target sequence as well as from the background. Claim 10, nor any of claims 11-20 which depend therefrom, recite any means by which the skilled artisan is to be able to discriminate between the two signals. Even if the target sequence and the background probes, and their respective signals are confined to an array, the use of an array (see claim 11) in and of its self does not automatically permit distinction between the two sources of signal. The skilled artisan would still need to be able to independently measure the amount of signal from both sources in order to adjust for any background noise or signal. The method, as presently claimed, does not accord the skilled artisan such means of discrimination that are essential to practicing the claimed invention.

The claimed method does not recite any conditions under which the hybridization reaction is to take place, yet the conditions under which a hybridization reaction occurs is critical to the skilled artisan obtaining useful information. As set forth in Carrico, (US Patent 5,200,313) the extent and specificity of hybridization is affected by the following principal conditions:

1. The purity of the nucleic acid preparation.

2. Base compositions of the probe - G-C base pairs will exhibit greater thermal stability than A-T or A-U base pairs. Thus, hybridizations involving higher G-C content will be stable at higher temperatures.

3. Length of homologous base sequences- Any short sequence of bases (e.g., less than 6 bases), has a high degree of probability of being present in many nucleic acids. Thus, little or no specificity can be attained in hybridizations involving such short sequences. From a practical standpoint, a homologous probe sequence will often be between 300 and 1000 nucleotides.

4. Ionic strength- The rate of reannealing increases as the ionic strength of the incubation solution increases. Thermal stability of hybrids also increases.

5. Incubation temperature- Optimal reannealing occurs at a temperature about 25 - 30 °C below the melting temperature for a given duplex. Incubation at temperatures significantly below the optimum allows less related base sequences to hybridize.

6. Nucleic acid concentration and incubation time- Normally, to drive the reaction towards hybridization, one of the hybridizable sample nucleic acid or probe nucleic acid will be present in excess, usually 100 fold excess or greater.

7. Denaturing reagents- The presence of hydrogen bond-disrupting agents, such as formaldehyde and urea, increases the stringency of hybridization.

8. Incubation- The longer the incubation time, the more complete will be the hybridization.

9. Volume exclusion agents- The presence of these agents, as exemplified by dextran and dextran sulfate, are thought to increase the effective concentrations of the hybridizing elements thereby increasing the rate of resulting hybridizations.

Further, subjecting the resultant hybridization product to repeated washes or rinses in heated solutions will remove non-hybridized probe. The use of solutions of decreasing ionic strength, and increasing temperature, e.g., 0.1X SSC for 30 minutes at 65 °C, will, with increasing effectiveness, remove non-fully complementary hybridization products.

Neither the claims nor the specification set forth in sufficient detail an enabling disclosure whereby one of skill in the art would be able to perform the claimed assay without having to take such issues into consideration.

Method claims 21-29, like that of claims 10-20, are not adequately enabled by the disclosure. As presently worded, one is to "estimate background noise in a nucleic acid hybridization assay," yet the only active method step recited is the subtraction of background signal from observed signal. Clearly, one of skill in the art would need to perform a plethora of method steps in order to arrive at two values of signal. As presently worded, one is to "estimate background noise," yet as can be seen in the active method step, such is already achieved prior to the method step as the skilled artisan is required to subtract the background noise from the

observed signal. The method does not set forth any active method steps whereby one of skill in the art actually arrives at a determination of the background noise in a nucleic acid hybridization assay. While claims 22-29 set forth characteristics of probes to be used in the assay, such does not overcome the failings of the claimed method to recite adequate method steps. As presently worded the method of claims 22-29 is to be practiced without any method steps that result in the estimation of background signal- the goal of the claimed method. Such seems a very implausible. While dependent claims set forth a variety of oligonucleotide sequences that are to be used, it is not clear how these various reagents are to be brought together in a common assay format such that the intended result can be realized. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

> " '[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').
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> *****
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> "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (starting, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.
> "It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385,

> 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

Claim 33 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. As presently worded claim 33 has sufficient breadth of scope so to encompass any probe that would detect any target nucleic acid, be it known or unknown to one of skill in the art at the time the subject application was filed. Further, the kit of claim 33 also encompasses any "background features," which have been interpreted for purposes of examination as encompassing non-target nucleic acid probes. In order to synthesize these "background features" the skilled artisan would need to have previously determined which sequences may well be expected to be encountered when performing a hybridization assay with a variety of nucleic acid sources, including the use of genomic sequences which, by default, would be comprised of innumerable other sequences, any one of which potentially possessing a region that would be complimentary to the background features. In support of this position, attention is directed to the decision of *Vas-Cath inc. V. Mahurkar* 19 USPQ2d 1111 (CAFC, 1991):

> This court in *Wilder* (and the CCPA before it) clearly recognized, and we hereby reaffirm, that 35 USC 112, first paragraph, requires a "written description of the invention" which is separate and distinct from the enablement requirement. The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the "applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

In view of the limited description of target sequences provided, the specification does not reasonably convey that applicant had any or all such target sequences, nor any or all background features that would compliment such target sequences, in their possession at the time of filing.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10-20 and 30-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 is indefinite with respect to just which "feature" is intended by the reference to "said feature." Upon review of the claim it is noted that there are "features" generally, as well as "hybridization features" and "background features." Claims 11-20, which depend from said claim 10, fail to overcome this issue and are similarly indefinite.

Claim 30 is indefinite with respect to just what constitutes "test-background probes" and "standard-background probes." Claims 31 and 32, that depend from said claim 30 fail to overcome this issue and are similarly indefinite.

Claims 10-32 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are:

(I) With respect to clams 10-20: (a) how the skilled artisan is to label that which is only suspected of being present (the target sequence) when the aliquot of sample analyte may well contain any number of contaminants and/or non-target sequences; (b) how the skilled artisan is to differentially detect the signal from the target and various non-target probes or features; (c) how unbound features and/or detectable label is removed from the assay mixture; and (d) how the various sequences set forth in claims 16-18, as well as nucleic acid analogs as well as abasic phosphodiester or modified nucleotidic units are made and used in the method of claim 10;

(II) With respect to claims 21-29: (a) how the nucleic acid assay is to be performed, e.g., when conducting *in situ* hybridization, PCR, LCR, array format, etc.; (b) how one is to differentially detect the target signal and non-target originating signals; and (c) how the various sequences set forth in claims 25-28, as well as nucleic acid analogs as well as abasic phosphodiester or modified nucleotidic units are made and used in the method of claim 21; and

(III) With respect to method claims 30-32: (a) how the nucleic acid assay is to be performed, e.g., when conducting *in situ* hybridization, PCR, LCR, array format, etc.; (b) how one is to differentially detect the target signal and non-target originating signals; and (c) what is the composition of the various features and under what conditions are they used.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (703) 308-3978. The examiner can normally be reached on Monday through Thursday from between the hours of 6:30 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152. The fax phone number for the organization where this application or proceeding is assigned is (703) 305-7230.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

B. L. Sisson

BRADLEY L. SISSON
PRIMARY EXAMINER
GROUP ~~1800~~ 1650
4/21/2000